L10 ANSWER 4 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2004:233875 USPATFULL
TITLE: DHA-pharmaceutical agent conjugates of taxanes
INVENTOR(S): Shashoua, Victor E., Brookline, MA, UNITED STATES
Swindell, Charles E., Merion, PA, UNITED STATES
Webb, Nigel L., Bryn Mawr, PA, UNITED STATES
Bradley, Matthews O., Laytonsville, MD, UNITED STATES
PATENT ASSIGNEE(S): Protarga, Inc., King of Prussia, PA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004180949	A1	20040916
APPLICATION INFO.:	US 2003-618884	A1	20030714 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-846838, filed on 1 May 2001, GRANTED, Pat. No. US 6602902 Continuation of Ser. No. US 1998-135291, filed on 17 Aug 1998, ABANDONED Continuation of Ser. No. US 1996-651312, filed on 22 May 1996, GRANTED, Pat. No. US 5795909
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 2440
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides conjugates of cis-docosahexaenoic acid and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.

SUMM . . . antidiabetic; antidiarrheal; antidiuretic; antidote; anti-emetic; anti-epileptic; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, **topical**; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiobessional agent; antiparasitic; antiparkinsonian; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy;. . .

SUMM . . . including adipose tissue, cartilage, connective tissue, cuticle, dermis, epidermis, epithelium, fascia, hair follicle, ligament, bone marrow, melanin, melanocyte, mucous membrane, **skin**, soft tissue, synovial capsule and tendon.

DETD [0147] Anti-infective, **topical**: Alcohol; Aminacrine Hydrochloride; Benzethonium Chloride; Bithionolate Sodium; Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridinium Chloride; Chlorhexidine Hydrochloride; Clioquinol; Domiphen Bromide; Fenticlor;. . .

DETD . . . Acid; Ipodate Calcium; Ipodate Sodium; Isosulfan Blue; Leukocyte Typing Serum; Lidofenin; Mebrofenin; Meglumine; Metrizamide; Metrizoate Sodium; Metyrapone; Metyrapone Tartrate; Mumps **Skin** Test Antigen; Pentetic Acid; Propyliodone; Quinaldine Blue; Schick Test Control; Sermorelin Acetate; Sodium Iodide I 123; Sprodiamide; Stannous Pyrophosphate; Stannous. . .

DETD . . . ersofermin; erythritol; esuprone; etanidazole; etanterol; ethacizin; ethinylestradiol; etizolam; etodolac; etoposide phosphate; etrabamine; everninomicin; examorelin; exemestane; fadrozole; faeriefungin; famciclovir; fampridine; fantofarone; **faropenem**; fasidotril; fasudil; fazarabine; fedotozine; felbamate; fenofibrate; fenoldopam; fenretinide; fenspiride; fenticonazole; fepradinol; ferpifosate sodium; ferristene; ferrixan; ferumoxsil; fexofenadine;

flavopiridol; flecainide; flerobuterol;. . .
DETD . . . anticoagulant; anticoccidal; antidiabetic; antidiarrheal; antidiuretic; antidote; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antithypotensive; anti-infective; anti-infective, **topical**; anti-inflanmmatory; antikeratinizing agent; antimalarial; antimicrobial; antimitotic; antimycotic, antineoplastic, antineutropenic, antiparasitic; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy; antiprotozoal; antipruritic; antipsoriatic; antirheumatic; antischistosomal;. . .
DETD . . . effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, **topical**, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred.

L10 ANSWER 5 OF 16 USPATFULL on STN
ACCESSION NUMBER: 2004:139413 USPATFULL
TITLE: Fatty acid-pharmaceutical agent conjugates
INVENTOR(S): Webb, Nigel L., Bryn Mawr, PA, UNITED STATES
Bradley, Matthews O., Laytonsville, MD, UNITED STATES
Swindell, Charles S., Merion, PA, UNITED STATES
Shashoua, Victor E., Brookline, MA, UNITED STATES
PATENT ASSIGNEE(S): Protarga Pharmaceuticals, Inc., King of Prussia, PA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004106589	A1	20040603
APPLICATION INFO.:	US 2003-455250	A1	20030605 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-730450, filed on 5 Dec 2000, GRANTED, Pat. No. US 6576636 Continuation of Ser. No. US 1996-651428, filed on 22 May 1996, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 2524
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides conjugates of fatty acids and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.
SUMM . . . including adipose tissue, cartilage, connective tissue, cuticle, dermis, epidermis, epithelium, fascia, hair follicle, ligament, bone marrow, melanin, melanocyte, mucous membrane, **skin**, soft tissue, synovial capsule and tendon.
SUMM . . . antidiabetic; antidiarrheal; antidiuretic; antidote; anti-emetic; anti-epileptic; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, **topical**; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiobessional agent; antiparasitic; antiparkinsonian; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy;. . .
DETD [0155] Anti-infective, **topical**: Alcohol; Aminacrine Hydrochloride; Benzethonium Chloride; Bithionolate Sodium;

Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridinium Chloride: Chlorhexidine Hydrochloride; Clioquinol; Domiphen Bromide; Fenticlor;. . .

DETD . . . Acid; Ipodate Calcium; Ipodate Sodium; Isosulfan Blue; Leukocyte Typing Serum; Lidofenin; Mebrofenin; Meglumine; Metrizamide; Metrizoate Sodium; Metyrapone; Metyrapone Tartrate; Mumps **Skin** Test Antigen; Pentetic Acid; Propyliodone; Quinaldine Blue; Schick Test Control; Sermorelin Acetate; Sodium Iodide 1123; Sprodiamide; Stannous Pyrophosphate; Stannous Sulfur. . .

DETD . . . ersofermin; erythritol; esuprone; etanidazole; etanterol; ethacizin; ethinylestradiol; etizolam; etodolac; etoposide phosphate; etrabamine; eveminomicin; examorelin; exemestane; fadrozole; faeriefungin; famciclovir; fampridine; fantofarone; **faropenem**; fasidotril; fasudil; fazarabine; fedotozine; felbarnate; fenofibrate; fenoldopam; fenretinide; fenspiride; fenticonazole; fepradinol; ferpifosate sodium; ferristene; ferrixan; ferumoxsil; fexofenadine; flavopiridol; flecainide; flerobuterol;. . .

DETD . . . anticholinergic; anticoagulant; anticoccidal; antidiabetic; antidiarrheal; antidiuretic; antidote; anti-estrogen; antifibrinolytic; antifungal; antiglaucomaagent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, **topical**; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimitotic; antimycotic, antineoplastic, antineutropenic, antiparasitic; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy; antiprotozoal; antipruritic; antipsoriatic; antirheumatic; antischistosomal;. . .

DETD . . . effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, **topical**, nasal, transdermal, intradermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred.

L10 ANSWER 11 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2003:85867 USPATFULL

TITLE: Oral delivery formulation

INVENTOR(S): Compton, Bruce Jon, Lexington, MA, UNITED STATES
Solari, Nancy E., West Newton, MA, UNITED STATES
Flangan, Margaret A., Stow, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003059471	A1	20030327
APPLICATION INFO.:	US 2001-997277	A1	20011129 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-55560, filed on 6 Apr 1998, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-69501P	19971215 (60)
	US 1998-73867P	19980204 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Stephen J Gaudet, 68H Stiles Road, Salem, NH, 03079

NUMBER OF CLAIMS: 42

EXEMPLARY CLAIM: 1

LINE COUNT: 2950

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Flakes containing drugs and methods for forming and using such flakes are provided.

SUMM . . . the seedy fibrous fruit texture masks the grittiness of the drug. The problem of grittiness also is evidenced in certain **topical** formulations. **Topical** formulations which

contain particles of drugs (or particles containing drugs) have an unpleasant gritty feel when applied to the **skin**.

SUMM . . . and swallowing. There also exists a need for a drug delivery system which is adaptable to all formats, including oral, **topical**, injectable, and other delivery formats. There also is a need for a drug delivery system that can permit adjustment of. . .

SUMM . . . form. The oral dosage form can be a semi-solid food. In another embodiment, the pharmaceutical preparation is formulated as a **topical** preparation. The **topical** preparation can contain an agent that is non-suitable for oral ingestion. In still another embodiment, the pharmaceutical preparation is formulated. . .

SUMM . . . discrete sizes to achieve a pulsed-type release, etc. The flakes can be relatively large so as to lend themselves to **topical** and oral delivery formats or can be extremely small, permitting them to be injected.

SUMM . . . can act as a delivery vehicle for existing microparticles. Such a delivery vehicle would be particularly useful for oral preparations, **topical** preparations, and in other circumstances as will be apparent to those of ordinary skill in the art.

SUMM [0048] The flakes also can be used in **topical** formulations. The flakes will provide a smooth, non-gritty coating on the **skin**, which can be used for delivering **topically** drugs contained in or attached to the flakes. Such **topical** preparations include virtually all of the known drugs presently delivered **topically**, but never before delivered as part of a flake. In addition, the flakes are particularly suited for the delivery of. . . any side effects for such sunscreen agents. The agent is held on the flake and is not released into the **skin**. The same benefit can be obtained when using flakes according to the invention to apply an insecticide. The insecticide can be covalently attached to the flakes which are **topically** applied as a smooth layer on the **skin**. Because the insecticides are covalently attached to the flakes, they are present for exerting the desired action, but they are not released generally in high dose into the **skin**, thereby avoiding potential unwanted side effects. Such sunscreen agents and insecticides on flakes also are desirable as the flakes themselves act as a smooth lubricant when applying the agents to the **skin**.

SUMM [0049] In **topical** preparations, the flakes, in general, are lubricating and therefore can prevent chafing of **skin** against **skin** or clothing against **skin**, as an additional benefit.

SUMM . . . conveniently delivered. The feel of such flakes is superior to the feel of the microparticles of the prior art. Such **topical** preparations can include agents for treating genital warts, kaposi sarcoma, actinic keratosis and **skin** cancers in general.

SUMM [0051] The **topical** preparations of the invention also can be used for applying wound healing agents to the **skin**. The wound healing agents can be attached to, coated on, or contained within the flakes of the invention, which can be applied **topically**.

SUMM . . . of the invention thus can be included in any of the prior art forms used for administering drugs, including implants, **topical** preparations, inhalable preparations, suppositories, ocular formulations, oral formulations and the like, which are well known. In certain of the preparations according to the invention, such as **topical** preparations, there may be included agents which are not suitable for oral ingestion. Such agents include creams, lubricants and the. . .

SUMM [0153] Anti-infective, **topical**: Alcohol; Aminacrine Hydrochloride; Benzethonium Chloride : Bithionolate Sodium; Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridinium Chloride :Chlorhexidine Hydrochloride; Clioquinol; Domiphen Bromide;. . .

SUMM . . . Acid; Ipodate Calcium; Ipodate Sodium; Isosulfan Blue; Leukocyte Typing Serum; Lidofenin; Mebrofenin; Meglumine; Metrizamide;

Metrizoate Sodium; Metyrapone; Metyrapone Tartrate; Mumps **Skin** Test Antigen; Pentetic Acid; Propyliodone; Quinaldine Blue; Schick Test Control; Sermorelin Acetate; Sodium Iodide I 123; Sprodiamide; Stannous Pyrophosphate; Stannous. . .

SUMM . . . ersofermin; erythritol; esuprone; etanidazole; etanterol; ethacizin; ethinylestradiol; etizolam; etodolac; etoposide phosphate; etrabamine; eveminomicin; examorelin; exemestane; fadrozole; faeriefungin; famciclovir; fampridine; fantofarone; **faropenem**; fasidotril; fasudil; fazarabine; fedotozine; felbamate; fenofibrate; fenoldopam; fenretinide; fenspiride; fenticonazole; fepradinol; ferpifosate sodium; ferristene; ferrixan; ferumoxsil; fexofenadine; flavopiridol; flecainide; flerobuterol;. . .

SUMM . . . effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, **topical**, nasal, transdermal, intradermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred.

CLM What is claimed is:

. . . preparation of claim 13 formulated as a dosage form, selected from the group consisting of: an oral dosage form, a **topical** dosage form and an implantable dosage form.

L10 ANSWER 14 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2002:17328 USPATFULL

TITLE: Dha-pharmaceutical agent conjugates of taxanes

INVENTOR(S): Shashoua, Victor, Brookline, MA, UNITED STATES
Swindell, Charles, Merion, PA, UNITED STATES
Webb, Nigel, Bryn Mawr, PA, UNITED STATES
Bradley, Matthews, Layton, PA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002010208	A1	20020124
	US 6602902	B2	20030805
APPLICATION INFO.:	US 2001-846838	A1	20010501 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1998-135291, filed on 17 Aug 1998, ABANDONED Continuation of Ser. No. US 1996-651312, filed on 22 May 1996, GRANTED, Pat. No. US 5795909

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Edward R. Gates, Esq., Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210

NUMBER OF CLAIMS: 19

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 14 Drawing Page(s)

LINE COUNT: 2437

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides conjugates of cis-docosahexaenoic acid and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.

SUMM . . . antidiabetic; antidiarrheal; antidiuretic; antidote; anti-emetic; anti-epileptic; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, **topical**; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimigraine; antirlitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiobessional agent; antiparasitic; antiparkinsonian; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy;. . .

SUMM . . . including adipose tissue, cartilage, connective tissue, cuticle, dermis, epidermis, epithelium, fascia, hair follicle, ligament, bone marrow, melanin, melanocyte, mucous membrane, **skin**, soft tissue, synovial capsule and tendon.

DETD [0144] Anti-infective, **topical**: Alcohol; Aminacrine Hydrochloride; Benzethonium Chloride: Bithionolate Sodium; Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridiniurn Chloride: Chlorhexidine Hydrochloride; Clioquinol, Domiphen Bromide; Fenticlor;. . .

DETD . . . Acid; Ipodate Calcium; Ipodate Sodium; Isosulfan Blue; Leukocyte Typing Serum; Lidofenin; Mebrofenin; Meglumine; Metrizamide; Metrizoate Sodium; Metyrapone; Metyrapone Tartrate; Mumps **Skin** Test Antigen; Pentetic Acid; Propyliodone; Quinaldine Blue; Schick Test Control; Sermorelin Acetate; Sodium Iodide I 123; Sprodiamide; Stannous Pyrophosphate; Stannous. . .

DETD . . . ersofermin; erythiritol; esuprone; etanidazole; etanterol; ethacizin; ethinylestradiol; etizolam; etodolac; etoposide phosphate; etrabamine; everninomicin; examorelin; exemestane; fadrozole; faeriefungin; famnciclovir; fampridine; fantofarone; **faropenem** ; fasidotril; fasudil; fazarabine; fedotozine; felbamate; fenofibrate; fenoldopam; fenretinide; fenspiride; fenticonazole; fepradinol; ferpifosate sodium; ferristene; ferrixan; ferumoxsil; fexofenadine; flavopiridol; flecainide; flerobuterol;. . .

DETD . . . anticoagulant; anticoccidal; antidiabetic; antidiarrheal; antidiuretic; antidote; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, **topical**; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimitotic; antimycotic, antineoplastic, antineutropenic, antiparasitic; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy; antiprotozoal; antipruritic; antipsoriatic; antirheumatic; antischistosomal;. . .

DETD . . . effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, **topical**, nasal, transdermnal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred.

L10 ANSWER 15 OF 16 USPATFULL on STN

ACCESSION NUMBER: 2001:90260 USPATFULL

TITLE: Fatty acid-pharmaceutical agent conjugates

INVENTOR(S): Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
Swindell, Charles S., Merion, PA, United States
Shashoua, Victor E., Brookline, MA, United States

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001002404	A1	20010531
	US 6576636	B2	20030610
APPLICATION INFO.:	US 2000-730450	A1	20001205 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1996-651428, filed on 22 May 1996, ABANDONED

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: Edward R. Gates, Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA, 02210

NUMBER OF CLAIMS: 12

EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 14 Drawing Page(s)

LINE COUNT: 2511

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides conjugates of fatty acids and pharmaceutical agents useful in treating noncentral nervous system conditions. Methods for selectively targeting pharmaceutical agents to desired tissues are provided.

SUMM . . . including adipose tissue, cartilage, connective tissue, cuticle, dermis, epidermis, epithelium, fascia, hair follicle, ligament, bone marrow, melanin, melanocyte, mucous membrane, **skin**, soft tissue, synovial capsule and tendon.

SUMM . . . antidepressant; antidiabetic; antidiarrheal; antidiuretic; antidote; anti-emetic; anti-epileptic; anti-estrogen; antifibrinolytic; antifungal; antiglaucomaagent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, **topical**; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimigraine; antimitotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiobessional agent; antiparasitic; antiparkinsonian; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy;. . .

DETD [0150] Anti-infective, **topical**: Alcohol; Aminacrine Hydrochloride; Benzethonium Chloride: Bithionolate Sodium; Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridinium Chloride: Chlorhexidine Hydrochloride; Clioquinol; Domiphen Bromide; Fenticlor;. . .

DETD . . . Acid; Ipodate Calcium; Ipodate Sodium; Isosulfan Blue; Leukocyte Typing Serum; Lidofenin; Mebrofenin; Meglumine; Metrizamide; Metrizoate Sodium; Metyrapone; Metyrapone Tartrate; Mumps **Skin** Test Antigen; Pentetic Acid; Propyliodone; Quinaldine Blue; Schick Test Control; Sermorelin Acetate; Sodium Iodide I 123; Sprodiamide; Stannous Pyrophosphate; Stannous. . .

DETD . . . ersofermin; erythritol; esuprone; etanidazole; etanterol; ethacizin; ethinylestradiol; etizolam; etodolac; etoposide phosphate; etrabamine; everninomicin; examorelin; exemestane; fadrozole; faeriefungin; famciclovir; fampridine; fantofarone; **faropenem**; fasidotril; fasudil; fazarabine; fedotozine; felbamate; fenofibrate; fenoldopam; fenretinide; fenspiride; fenticonazole; fepradinol; ferpifosate sodium; ferristene; ferrixan; ferumoxsil; fexofenadine; flavopiridol; flecainide; flerobuterol;. . .

DETD . . . anticholinergic; anticoagulant; anticoccidal; antidiabetic; antidiarrheal; antidiuretic; antidote; anti-estrogen; antifibrinolytic; antifungal; antiglaucomaagent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, **topical**; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimitotic; antimycotic, antineoplastic. antineutropenic, antiparasitic; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy; antiprotozoal; antipruritic; antipsoriatic; antirheumatic; antischistosomal;. . .

DETD . . . effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, **topical**, nasal, transdermal, intradermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred.

L10 ANSWER 16 OF 16 USPATFULL on STN
ACCESSION NUMBER: 1998:98932 USPATFULL
TITLE: DHA-pharmaceutical agent conjugates of taxanes
INVENTOR(S): Shashoua, Victor E., Brookline, MA, United States
Swindell, Charles S., Merion, PA, United States
Webb, Nigel L., Bryn Mawr, PA, United States
Bradley, Matthews O., Laytonsville, MD, United States
PATENT ASSIGNEE(S): Neuromedica, Inc., Conshohocken, PA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 5795909		19980818	
APPLICATION INFO.:	US 1996-651312		19960522	(8)

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Jarvis, William R. A.
LEGAL REPRESENTATIVE: Wolf, Greenfield & Sacks, P.C.
NUMBER OF CLAIMS: 12
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 27 Drawing Figure(s); 14 Drawing Page(s)
LINE COUNT: 2451
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The invention provides conjugates of cis-docosahexaenoic acid and taxanes useful in treating cell proliferative disorders. Conjugates of paclitaxel and docetaxel are preferred.

SUMM . . . antidiabetic; antidiarrheal; antidiuretic; antidote; anti-emetic; anti-epileptic; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, **topical**; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimigraine; antirditotic; antimycotic, antinauseant, antineoplastic, antineutropenic, antiobessional agent; antiparasitic; antiparkinsonian; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy;. . .

SUMM . . . including adipose tissue, cartilage, connective tissue, cuticle, dermis, epidermis, epithelium, fascia, hair follicle, ligament, bone marrow, melanin, melanocyte, mucous membrane, **skin**, soft tissue, synovial capsule and tendon.

DETD Anti-infective, **topical**: Alcohol; Aminacrine Hydrochloride; Benzethonium Chloride: Bithionolate Sodium; Bromchlorenone; Carbamide Peroxide; Cetalkonium Chloride; Cetylpyridinium Chloride: Chlorhexidine Hydrochloride; Clioquinol,. Domiphen Bromide; Fenticlor;. . .

DETD . . . Acid; Ipodate Calcium; Ipodate Sodium; Isosulfan Blue; Leukocyte Typing Serum; Lidofenin; Mebrofenin; Meglumine; Metrizamide; Metrizoate Sodium; Metyrapone; Metyrapone Tartrate; Mumps **Skin** Test Antigen; Pentetic Acid; Propyliodone; Quinaldine Blue; Schick Test Control; Sermorelin Acetate; Sodium Iodide I 123; Sprodiamide; Stannous Pyrophosphate; Stannous. . .

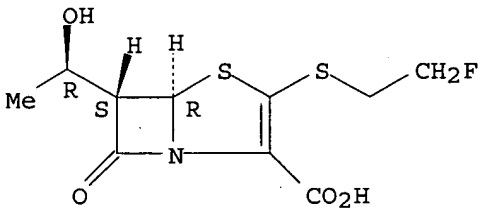
DETD . . . ersofermin; erytlritol; esuprone; etanidazole; etanterol; ethacizin; ethinylestradiol; etizolam; etodolac; etoposide phosphate; etrabamine; everninomicin; examorelin; exemestane; fadrozole; faeriefungin; famciclovir; fampridine; fantofarone; **faropenem**; fasidotril; fasudil; fazarabine; fedotozine; felbamate; fenofibrate; fenoldopam; fenretinide; fenspiride; fenticonazole; fepradinol; ferpifosate sodium; ferristene; ferrixan; ferumoxsil; fexofenadine; flavopiridol; flecainide; flerobuterol;. . .

DETD . . . anticoagulant; anticoccidal; antidiabetic; antidiarrheal; antidiuretic; antidote; anti-estrogen; antifibrinolytic; antifungal; antiglaucoma agent; antihemophilic; antihemorrhagic; antihistamine; antihyperlipidemia; antihyperlipoproteinemic; antihypertensive; antihypotensive; anti-infective; anti-infective, **topical**; anti-inflammatory; antikeratinizing agent; antimalarial; antimicrobial; antimitotic; antimycotic, antineoplastic, antineutropenic, antiparasitic; antiperistaltic, antipneumocystic; antiproliferative; antiprostatic hypertrophy; antiprotozoal; antipruritic; antipsoriatic; antirheumatic; antischistosomal;. . .

DETD . . . effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, sublingual, **topical**, nasal, transdermal or parenteral routes. The term "parenteral" includes subcutaneous, intravenous, intramuscular, or infusion. Intravenous routes are preferred.

L4 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2005 ACS on STN
RN **85905-06-2** REGISTRY
CN 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[(2-fluoroethyl)thio]-6-(1-hydroxyethyl)-7-oxo-, [5R-[5α,6α(R*)]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C10 H12 F N O4 S2
CI COM
LC STN Files: CA, CAPLUS, PROUSDDR, TOXCENTER, USPATFULL
DT.CA CAplus document type: Journal; Patent
RL.P Roles from patents: PREP (Preparation)
RL.NP Roles from non-patents: BIOL (Biological study); PREP (Preparation)

Absolute stereochemistry.

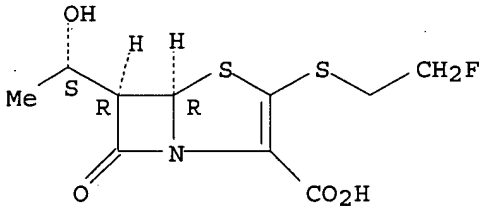


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 1 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 190960-20-4 REGISTRY
ED Entered STN: 10 Jul 1997
CN 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[(2-fluoroethyl)thio]-6-(1-hydroxyethyl)-7-oxo-, [5R-[5α,6β(S*)]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C10 H12 F N O4 S2
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



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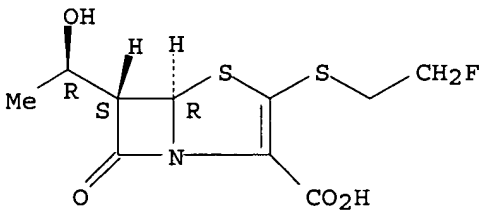
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 2 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 87131-59-7 REGISTRY
ED Entered STN: 16 Nov 1984
CN 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[(2-fluoroethyl)thio]-6-(1-hydroxyethyl)-7-oxo-, monopotassium salt, [5R-[5α,6α(R*)]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C10 H12 F N O4 S2 . K
LC STN Files: CA, CAPLUS, PROUSDDR, TOXCENTER, USPATFULL
CRN (85905-06-2)

Absolute stereochemistry.



● K

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

Blessing

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RN 85905-06-2 REGISTRY
ED Entered STN: 16 Nov 1984
CN 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[(2-fluoroethyl)thio]-6-(1-hydroxyethyl)-7-oxo-, [5R-[5α,6α(R*)]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
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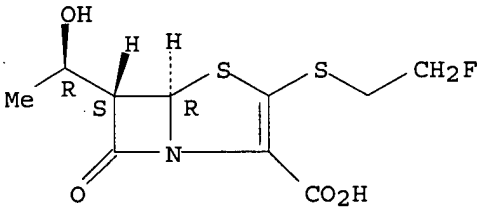
CI COM
LC STN Files: CA, CAPLUS, PROUSDDR, TOXCENTER, USPATFULL

Absolute stereochemistry.

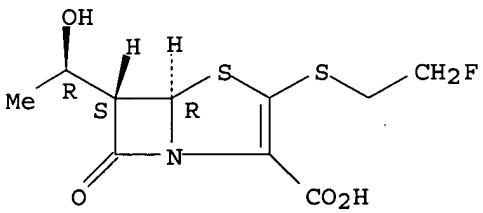


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L2 ANSWER 4 OF 4 REGISTRY COPYRIGHT 2005 ACS on STN
RN 85905-05-1 REGISTRY
ED Entered STN: 16 Nov 1984
CN 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 3-[(2-fluoroethyl)thio]-6-(1-hydroxyethyl)-7-oxo-, monosodium salt, [5R-[5α,6α(R*)]]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C10 H12 F N O4 S2 . Na
LC STN Files: BEILSTEIN*, CA, CAPLUS, CASREACT, PROUSDDR, TOXCENTER, USPATFULL
(*File contains numerically searchable property data)
CRN (85905-06-2)

Absolute stereochemistry.



● Na

Blessing

10758217

11 REFERENCES IN FILE CA (1907 TO DATE)
11 REFERENCES IN FILE CAPLUS (1907 TO DATE)

Blessing

10. The composition of any one of claims 1 to 8, for dental external use.

Description

FIELD OF THE INVENTION

[0001] The present invention relates to pharmaceutical compositions for use in dermatological, ophthalmologic, otolaryngologic, dental/oral surgical and urogenital fields, and more specifically to the use of penem antibiotics for topical administration.

PRIOR ART

[0002] Ointments are used for topical administration to treat various diseases due to their convenience of administration and portability.

[0003] Therapeutic agents comprising antibiotics in an ointment base are useful for treating local inflammatory or pyogenic diseases caused by bacterial infection. There is a demand for these ointments, with a number being available.

[0004] For example, ointments containing aminoglycoside, tetracycline and chloramphenicol antibiotics are commonly used for inflammatory or pyogenic diseases in dermatological, ophthalmologic, otolaryngologic, dental/oral surgical and urogenital fields. Specific examples include commercially available dermatological agents for pyogenic diseases, based on aminoglycoside antibiotics such as kanamycin monosulfate ointments, tetracycline antibiotics such as tetracycline hydrochloride ointments and chloramphenicol antibiotics such as chloramphenicol ointments, as well as commercially available ophthalmic ointments based on macrolide antibiotics such as pimaricin formulations. Ointments containing tetracycline hydrochloride as a tetracycline antibiotic and hydrocortisone acetate are commercially available for dental/oral surgical application.

[0005] The active component in antibiotic ointments should be incorporated in a stable form. Japanese Patent Publication (Kokoku) No. 12728/89 describes a composition for topical administration as an external dental agent. In this composition, a magnesium compound is employed to a hydrogel comprising minocycline or a pharmaceutically acceptable salt thereof as a tetracycline antibiotic in a water-soluble polymer compound and a polyhydric alcohol to stabilize the antibiotic.

[0006] On the other hand, penem compounds are non-natural .beta.-lactam compounds designed based on the concept of combining the structures of penicillin and cephalosporin (e.g. see Woodward, R. B., In Recent Advances in the Chemistry of .beta.-Lactam Antibiotics; Elks, J., Ed; The Chemical Society; London, 1977; Spec. No. 28, pp. 167-180, Japanese Patent Public Disclosure (Kokai) Nos. 207387/86, 162694/88, 222486/85 and 119486/79), with the aim of creating a new range of antibiotics which have the broad antibacterial spectrum and high safety of penicillin antibiotics and cephem antibiotics belonging to .beta.-lactam antibiotics combined with the potent antibacterial activity and high stability to .beta.-lactamase of carbapenem antibiotics.

Currently, sodium (+)-(5R, 6S)-6-[(R)-1-hydroxyethyl]-7-oxo-3-[(R)-2-tetrahydrofuryl]-4-thia-1-azabi- cyclo[3.2.0]hepto-2-ene-2-carboxylate 2.5 hydrate (faropenem sodium, hereinafter referred to as Compound 1) is orally administated as a therapeutic agent for use in various infections. The penem compounds are reported to show potent antibacterial activity on not only methicillin-sensitive Staphylococcus aureus (MSSA), Streptococcus pyrogenes and Streptococcus pneumoniae but also gram-positive bacteria less susceptible to conventional .beta.-lactam agents such as penicillin-resistant Streptococcus pneumoniae (PRSP), stomatic Streptococcus spp. and Enterococcus sp. by virtue of the novel skeleton called penem ring. The broad-spectrum antibacterial activity covers gram-negative bacteria such as Haemophilus influenzae and anaerobics such as the genus Bacteroides (Antibiotics & Chemotherapy, Vol. 13, No. 10, pp. 74-80, 1997). They are also reported to exhibit potent antibacterial activity on not only pathogenic bacteria of periodontitis such as Porphyromonas gingivalis (Chemotherapy, Vol. 42, S-1, pp. 38-50, 1994) but also other strains which are becoming increasingly resistant, that cause dental infections (Chemotherapy, Vol. 45, No. 11, pp. 965-971, 1997).

[0007] However, penem compounds, like other .beta.-lactam compounds, are generally chemically labile to hydrolysis, oxidation, photoisomerization, etc., and no composition for topical administration has been known that exhibits their excellent efficacy against inflammatory or pyogenic diseases, or diseases caused by infection with resistant bacteria.

[0008] Furthermore, in formulating ointments, an active component has to be mixed homogeneously throughout a semisolid base. When an active component is in the form of crystals or a crystalline powder like penem antibiotics, it is difficult to achieve overall homogeneity simply by dispersing the component in a base. Therefore, the component must first be ground into fine particles or dissolved in solvent, before being kneaded with a base into an ointment. Pulverization of the component is necessary also in view of the resulting texture of the formulation.

[0009] However, no technique for use of a penem compound as a component of an ointment has hitherto been known.

SUMMARY OF THE INVENTION

[0010] Under the circumstances described above, the inventors conducted extensive studies to develop a method to topically administer penem antibiotics and pharmaceutically acceptable salts thereof which have a broad-spectrum and a potent antibacterial activity as well as being highly safe. As a result, the inventors have developed a highly safe antibacterial composition for topical administration in which the active component is incorporated in a stable form. The present invention has been accomplished based on the finding.

[0011] Accordingly, the present invention relates to an antibacterial composition for topical administration comprising a penem antibiotic or a pharmaceutically acceptable salt thereof incorporated in a non-aqueous base.

[0012] According to the present invention, very unstable penem antibiotics can be stably incorporated in a non-aqueous base such as hydrophobic polymer compounds to provide an antibacterial composition which can be widely used in dermatological, ophthalmologic, otolaryngologic, dental/oral surgical and urogenital fields.

[0013] Antibacterial compositions of the present invention may further contain various additives such as water-soluble or hydrophilic polymer compounds conferring thickening effects to provide various compositions for intended uses without affecting the stability of active components.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The composition of the present invention is basically a viscous liquid or paste-like composition comprising a penem antibiotic or a pharmaceutically acceptable salt thereof incorporated in a non-aqueous base, and it is typically formulated into an ointment. It is important that the base of a non-aqueous type is used to ensure the stability of the penem antibiotic.

[0015] Penem antibiotics used in the present invention are not specifically limited provided that they are antibacterially active, compatible to lesions and safe in view of irritability, sensitizing effect and oral toxicity, and that they are pharmaceutically acceptable. They may be either in the form of a free carboxylic acid or a pharmaceutically acceptable salt including salts with alkali or alkali earth metals such as sodium, potassium, calcium, magnesium or amino acids such as lysine or ammonium salts. Examples of such compounds other than the above Compound 1 include those in which the substituent at position 3 is 1,4-dioxane-2-yl, ethylsulphanyl, 3-tetrahydrofurylmethyl, methoxymethyl or ((aminocarbonyl)oxy)methyl or the like. The content of such a compound in the composition may be appropriately determined depending on the nature of the compound, the disease to be treated or other factors. For example, Compound 1 is incorporated at 10% by weight or less, normally 0.1 to 5% by weight expressed as free anhydride on the basis of the whole composition.

[0016] In order to formulate a penem antibiotic into an ointment, the active component must be incorporated into the composition in such a manner as to ensure the stability of the active component while assuring applicability or usability. In the present invention, proper stability can be ensured for penem antibiotics by using a non-aqueous base.

[0017] As used herein, "non-aqueous" base is a base which is substantially free from water. Thus, typical examples of non-aqueous bases are hydrophobic polymer compounds generally classified as hydrophobic ointment bases, such as oleaginous ointment bases consisting of hydrophobic polymers commonly used for ointments. Oleaginous ointment bases include, for example, hydrocarbon gel, paraffin, liquid paraffin, white petrolatum, petrolatum, microcrystalline wax, plant oils (vegetable oils), carnauba wax, beewax, stearic acid, stearyl alcohol, cacao butter, cetanol, hard fat, white ointment, simple ointment and ceresin.

[0018] Included in the non-aqueous bases used in the present invention are some emulsion bases which are free from any aqueous phase or film coating- or matrix-bases which are free from any aqueous phase. Emulsion ointment bases free from aqueous phase include hydrophilic petrolatum and purified lanolin. Film coatings and matrix bases free from any aqueous phase include acrylic resins which are commercially available under the trade name Eudragit (aminoalkyl methacrylate copolymer E, aminoalkyl methacrylate copolymer RS, methacrylic acid copolymer L, methacrylic acid copolymer S, ethyl acrylate-methyl methacrylate copolymer emulsion, available from Rohm Pharma, Germany) optionally in combination with plasticizers.

[0019] One or more of these bases are preferably used. Especially preferred are hydrocarbon gel, white petrolatum and Eudragit.

[0020] Neither hydrophilic bases in general nor many of the emulsion ointment bases, i.e. those comprising an aqueous phase, such as hydrophilic ointment and absorptive ointment will provide ointments which are capable of maintaining the activity of incorporated active components.

[0021] When the composition of the present invention is embodied as a pharmaceutical composition directly administered to a local site in the mouth for treating periodontitis, a high degree of viscosity will be required to provide a prolonged effect at the target site. In such a case, additives such as gelatinizers, thickening agents, viscosifiers, viscosity enhancers and elasticizers may be optionally added. Additives for this purpose include water-soluble or hydrophilic polymer compounds such as carmellose, carmellose sodium, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylic acid, sodium polyacrylate, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellul- ose, hydroxyethylcellulose, hydroxyethylmethylcellulose, xanthan gum, tragacanth gum, guar gum, locust bean gum, arabic gum, chitosan, sodium alginate, starches, gelatins, hydrophobically modified-hydroxypropylmethy- lcellulose (Sangelose, available from Sankyo Chemical). One or more of these compounds can be added at a proportion of 0.1 to 10% by weight, preferably 0.5 to 10% by weight on the basis of the whole composition to further enhance the thickening effect at the target site.

[0022] The water-soluble or hydrophilic polymer compounds may also be employed to facilitate the absorption of secreted fluids from body tissues and prevent any contamination at the location.

[0023] As long as the purposes and effects of the present invention are not compromised, other components such as conventional plasticizers, surfactants, perfumes, flavoring agents or other additives may be optionally employed in an amount which does not influence the stability of the active component.

[0024] Suitable plasticizers include triacetine, diacetyl ethylene glycol, diethyl sebacate, diethyl phthalate, dibutyl phthalate, diisopropyl adipate, dibutyl succinate. Suitable surfactants include polyoxyl stearate 40, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, Polysorbate, sucrose esters of fatty acids. Suitable flavoring agents include sodium, saccharin or the like. Stabilizers such as calcium disodium edetate or the like may also be used as judged appropriate.

[0025] The composition of the present invention may further contain appropriate amounts of perfumes such as menthol, carboxylic acids, anethole, eugenol, methyl salicylate, limonene, ocimene, citronellol, methyl acetate, methyl eugenol, vanillin, thymol, spearmint oil, peppermint oil, lemon oil, orange oil, rosemary oil, cinnamon oil, eucalyptus oil and pimento oil alone or in combination.

[0026] If necessary, higher alcohols, higher fatty acids, shellac-ethylcellulose, ethylcellulose, carnauba wax, hydroxypropylmethylcellulose acetate succinate and solubilizing agents therefor may be used alone or in combination to effect control of the release of the active component from the base or to mask the odor of the active component.

[0027] The composition of the present invention comprise a base selected from those which have been confirmed in terms of their stability, and hence, which may be applied by various application methods without being limited to any specific one. For example, the ointment is suitable for any

one of topical external application on the skin for the treatment of acne, urogenital application, oral application for the treatment of infectious periodontitis or the like.

[0028] In accordance with the present invention, it is also provided processes for preparing the composition of the invention.

[0029] The process of the invention is characterized in that a non-aqueous base is provided without any use of water in its preparation which would otherwise affect the stability of the active component. The process for preparing the composition of the present invention is described in detail below.

[0030] Three basic alternatives can be mentioned as methods for preparing the composition of the present invention, i.e., dispersion method, fusion method and slolubilizing method.

[0031] In the dispersion method, a homogeneous dispersion of the active component in a non-aqueous base is prepared by thoroughly grinding, pulverizing and kneading the active component, to make suitable the crystalline active component for topical administration. A preferred particle diameter of the active component is preferably 500 .mu.m or less, normally 100 .mu.m or less. For small scale production, the active component is mixed and thoroughly triturated with a portion of the base using an ointment slab and an ointment spatula or a mortar and a pestle. Subsequently, the rest of the base and other additives are added and trituration is continued until overall homogeneity is achieved. For large scale production, machines such as three roller machines, roll mills, kneaders, grinders or mixers are used. These machines may be used optionally under a reduced pressure or under heating. In such a case, the optimal stirring speed will be between 25 and 100 rpm and a preferred vacuum level ranges from 60 to 80 cmHg. A suitable heating temperature is between 35 to 60.degree. C. depending on the stability of the active component. If necessary, the resulted particles may be screened.

[0032] In the fusion method, since the active component is readily soluble in water, and its activity is lowered by hydrolysis, the active component is first wet-triturated in a non-aqueous base such as a small amount of liquid paraffin. Subsequently, the other components are successively admixed in an order that increases the ability of the component to solubilize the active component, to thereby finally accomplish overall homogeneity. Fusion may be carried out under heating and stirring, if necessary. A suitable heating temperature is between 35 to 60.degree. C. depending on the stability of the active component. An ointment jar and a water bath may be used for small scale production, while machines such as a three roller machine, grinders and mixers will be used in a water bath for large scale production. During the process, an optimal stirring speed is between 25 to 100 rpm and a preferred vacuum level is 60 to 80 cmHg. Particles may be filtered or screened, if necessary.

[0033] The solubilizing method comprises the use of a non-aqueous solvent compatible with the non-aqueous base since the active component is readily soluble in water and its activity is lowered by hydrolysis. For example, a solution of the active component in methanol or ethanol is kneaded with a non-aqueous base, optionally under heating or stirring. A suitable heating temperature is between 35 to 60.degree. C. depending on the stability of the active component. The solution in which the active component has been dissolved is mixed and thoroughly triturated with a portion of the base, then further triturated with the rest of the base and other additives to provide overall homogeneity. Mixing or trituration is performed with an ointment slab and an ointment spatula or a mortar and a pestle for small scale production. For large scale production, a three roller machine,

roller mills, kneaders, grinders and mixers or the like are used. These machines may be used optionally under reduced pressure and an optimal agitation speed is between 25 to 100 rpm and the vacuum level is preferably 60 to 80 cmHg. Optionally, particles may be filtered or screened.

[0034] The methods described above are preferably carried out under conditions which are free from not only water but also any other external factors which may potentially affect the stability of the active component. Such external factors include, for example, high temperatures, light and oxygen, which would all cause a deterioration in the active component.

[0035] The step of filling the composition into a container should also be carried out under conditions which are free from any of the stated external factors. Namely, the shape of the container should be capable of preventing contact with such external factors and also be able to properly maintain the stability of the active component of the composition. Specific examples include bottles or jars made from glass, plastics and synthetic resins, or tubes made from metals, plastics and laminates. To seal the container, a screw cap is used to effect closure for bottles and jars, or folding a metal tube filled from its bottom end or contact-bonding a similarly filled plastic tube between hot plates, or contact-bonding a similarly filled laminate tube under heat such as high frequency or supersonic wave can also be employed.

[0036] The shape of the container may be selected depending on the intended use. Thus, in addition to the shapes mentioned above, the container may have a shape which enables, for example, direct application or injection of the composition at various body sites. One example is a container designed to discharge the composition by a piston-like rod from an injection cylinder or a syringe made from plastic or synthetic resin.

EXAMPLES

[0037] The following examples further illustrate the present invention using Compound 1 without, however, limiting the same thereto.

Example 1

[0038]

1 Component % by weight Compound 1 2.5.sup.1) Hydrocarbon gel .sup.2) 97.5 .sup.1)2.0% as free anhydride (the same applies below) .sup.2)Plastibase, available from Bristol-Myers Squibb Co. (the same applies below).

[0039] 1) 2.0% as free anhydride (the same applies below)

[0040] 2) Plastibase, available from Bristol-Myers Squibb Co.(the same applies below).

[0041] Compound 1 was mixed with hydrocarbon gel to overall homogeneity to give the desired composition.

Example 2

[0042]

2 Component % by weight Compound 1 6.2.sup.3) Hydrocarbon gel 93.8 .sup.3)5.0% as free anhydride.

[0043] Compound 1 was mixed with hydrocarbon gel to overall homogeneity to give the desired composition.

Example 3

[0044]

3 Component % by weight Compound 1 12.4.sup.4) Hydrocarbon gel 87.6 .sup.4)10.0% as free anhydride.

[0045] Compound 1 was mixed with hydrocarbon gel to overall homogeneity to give the desired composition.

Example 4

[0046]

4 Component % by weight Compound 1 2.5 White petrolatum 97.5

[0047] Compound 1 was mixed with white petrolatum to overall homogeneity to give the desired composition.

Example 5

[0048]

5 Component % by weight Compound 1 2.5 Purified lanolin 97.5

[0049] Compound 1 was mixed with purified lanolin to overall homogeneity to give the desired composition.

Example 6

[0050]

6 Component % by weight Compound 1 2.5 Carmellose sodium 2.0 Hydrocarbon gel 95.5

[0051] Compound 1 was mixed with a dispersion of carmellose sodium in hydrocarbon gel to give the desired composition. This composition is particularly suitable for oral application as a therapeutic agent for periodontal diseases.

Example 7

[0052]

7 Component % by weight Compound 1 2.5 Xanthan gum 2.0 Hydrocarbon gel 95.5

[0053] Compound 1 was mixed with a dispersion of xanthan gum in hydrocarbon gel to give the desired composition. This composition is suitable for oral application as a therapeutic agent for periodontal diseases.

Example 8

[0054]

8 Component % by weight Compound 1 2.5 Liquid paraffin 0.2 Hydrocarbon gel 97.3

[0055] Compound 1 was wet-kneaded with liquid paraffin and then mixed with hydrocarbon gel to overall homogeneity to give the desired composition.

Example 9

[0056]

9 Component % by weight Compound 1 2.5 Ethanol 0.1 Hydrocarbon gel 97.4

[0057] Hydrocarbon gel was added in portions into a solution of Compound 1 in ethanol and mixed to overall homogeneity to give the desired composition.

Stability Test of Penem-Containing Composition

[0058] A plastic container filled with a composition containing Compound 1 prepared according to the 5 formulations of Examples 1, and 4 to 7 was sealed with a screw cap. The container was stored at 40.degree. C., 75% relative humidity (RH) for 1 month or 2 months or at room temperature for 1 month. Any observable change in the appearance of the composition was evaluated, and at the same time, the potency of the antibiotic was determined by high-performance liquid chromatography, from which the residual retention (%) to the initial potency was calculated.

[0059] Conditions for high-performance liquid chromatography were as follows. A stainless steel high-performance liquid chromatography column charged with octadecylsilylated silica gel was used. Column temperature was maintained at 40.degree. C. The mobile phase consisted of Solution A containing 45 mM potassium dihydrogenphosphate, 5 mM sodium monohydrogenphosphate and 5 mM tetra-n-butylammonium bromide and Solution B comprising a 1:1 mixture of Solution A and acetonitrile. The mobile phase initially contained 16% of Solution B, then once analysis was started, Solution B was gradually increased to 70% over 54 minutes. The flow rate was controlled so that the retention time of Compound 1 was 24 minutes. The detector used was a UV spectrophotometer at a wavelength of 240 nm.

[0060] As controls, the following formulations using hydrophilic bases were also tested in the same manner.

Control 1

[0061]

10 Component % by weight Compound 1 2.5.sup.1) Hydrophilic ointment 97.5 .sup.1)2.0% as free anhydride

[0062] Compound 1 was mixed with hydrophilic ointment to overall homogeneity to give the composition of Control 1.

Control 2

[0063]

11 Component % by weight Compound 1 2.5.sup.1) Absorptive ointment 97.5 .sup.1)2.0% as free anhydride

[0064] 1) 2.0% as free anhydride

[0065] Compound 1 was mixed with absorptive ointment to overall homogeneity to give the composition of Control 2.

[0066] Results are shown in Table 1.

12TABLE 1 Composition No. (Control No.) 1 2 3 4 5 (1) (2) Formulation (% by weight) Compound 1 2.5 2.5 2.5 2.5 2.5 2.5 2.5 Hydrocarbon gel 97.5 95.5 95.5 0 0 0 0 White peterolatum 0 0 0 97.5 0 0 0 Purified lanolin 0 0 0 0 97.5 0 0 Hydrophilic ointment 0 0 0 0 0 97.5 0 Absorptive ointment 0 0 0 0 0 0 97.5 Cannellose sodium 0 2.0 0 0 0 0 0 Xanthan gum 0 0 2.0 0 0 0 0 Stability test results Initial appearance White Yellowish Yellowish Yellowish Pale White White Semisolid white white white greenish Semisolid Semisolid Semisolid Semisolid Semisolid yellow Semisolid Storage for Appearance Yellowish Yellowish Slightly Slightly Yellow Pale Bright 1 month at after storage white white pale pale Semisolid yellow yellow 40.degree. C., 75% RH Semisolid Semisolid yellow yellow Semisolid Semisolid Semisolid Semisolid Storage for Appearance Yellowish Yellowish Slightly Slightly Yellow Pale Dark 2 months at after storage white white pale pale Semisolid yellow reddish 40.degree. C., 75% RH Semisolid Semisolid yellow yellow Semisolid yellow Semisolid Semisolid Semisolid Potency retention (%) 100 97 100 100 92 0 0 Storage for Appearance White Yellowish Yellowish Yellowish Pale Pale Bright 1 month at after storage Semisolid white white white greenish yellow reddish room Semisolid Semisolid Semisolid yellow Semisolid yellow temperature Semisolid Semisolid Potency 100 100 100 100 100 47 26 rentention (%)

[0067] As shown in Table 1, combinations of Compound 1 with non-aqueous bases such as hydrocarbon gel, white petrolatum and purified lanolin provided stable compositions, and their stability was not adversely affected even by the addition of water-soluble polymer compounds such as carmellose sodium and xanthan gum as thickening agents. In contrast, when a water-absorbing ointment or hydrophilic ointment with hydrophilicity was used as a base, the active component was inactivated after storage at 40.degree. C. for 2 months, or even after storage at room temperature for 1 month, and the properties of the composition were changed with a significant decrease in the residual titer of Compound 1 to generate many decomposition products including hydrolyzates,

hydrolytic isomerization products and cleavage products of Compound 1.

[0068] Thus, the compositions in which Compound 1 was admixed into a non-aqueous bases according to the present invention were stable, and their stability was not affected even by addition of a water-soluble polymer compound.

[0069] A similar stability was observed when the composition according to the formulation of Example 1 was stored at room temperature for 3 years.

Advantageous Effects of the Invention

[0070] According to the present invention, very unstable penem antibiotics can be formulated into a stable composition by using hydrophobic polymer compounds as bases without the stability of the active component being compromised by further addition of water-soluble polymer compounds, to thereby provide antibacterial compositions which can be widely used in dermatological, ophthalmologic, otolaryngologic, dental/oral surgical and urogenital fields.

* * * * *

Faropenem: A Representative of the Penem Class

In general, penems have demonstrated a broad spectrum of activity and high potency. However, as a consequence of wrongly aligning penems with carbapenems, issues associated with carbapenems, such as renal DHP stability, are often misapplied to the penem class. So far, in vitro studies of activity against antimicrobial-resistant clinical isolates and in vivo studies of stability to DHP and safety issues have indicated that, as a class, the penems have a favorable profile.

Faropenem (previously known as SUN5555, SY5555, WY49605, RU67655, ALP201, BLA 857, YM 044, farom, fropenem, and furopenem) is the most well-studied member of the penem class. Three forms of faropenem have been described: free acid, sodium salt, and daloxate prodrug derivative (Figure 3). Faropenem originally was synthesized as the sodium salt, but the oral bioavailability of this compound was only 20-30%. In contrast, the daloxate ester has an oral bioavailability of 70-80%.[19] This ester is hydrolyzed rapidly in vivo to release the active free acid. At the time of this writing, faropenem daloxate was in phase III clinical trials for the treatment of a range of community-acquired infections including respiratory tract infections.

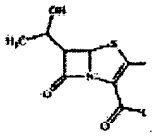


Figure 3. (click image to zoom) Structures of the three forms of faropenum.

Chemistry

Faropenem daloxate (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl-(5R,6S)-6-[(R)-1-hydroxyethyl]-7-oxo-3-[(R)-2-tetrahydrofuryl]-4-thia-1-aza-bicyclo [3,2,0]hept-2-ene-carboxylate) ($C_{17}H_{19}NO_8S$) exists as a single pure enantiomer with a molecular weight of 397.41 daltons. It is classed as an arylpenem, with the aryl side chain, a saturated, oxygen-containing tetrahydrofuran group, substituted at position 2 of the thiazoline nucleus.[3] The daloxate moiety of faropenem is attached by an ester link to C3of the thiazoline ring. Faropenem daloxate is a nonhygroscopic, yellowish white crystalline solid that is light sensitive and stable at pH 4 and 25°C.[41]

Mechanism of Action

As with other penems, faropenem induces bactericidal effects by binding to PBPs and inhibiting bacterial cell wall synthesis. These bactericidal effects were found to be affected by the nature of the tetrahydrofuran side chain, with an unsaturated derivative showing reduced activity compared with that of the saturated derivative (faropenem).[42] Faropenem is also less susceptible to the actions of DHP-1 than are the carbapenems imipenem and meropenem[41]; it has been proposed that the absence of a protonable group in the 2-side chain of faropenem, in contrast to the presence of such groups in the equivalent side chains of the carbapenems, is responsible for this phenomenon.[41] Finally, faropenem is resistant to the effects of many bacterial β-lactamases. This property is thought to be due to the 1-(R)-hydroxyethyl group at C6 of the bicyclic molecule.

In Vitro Activity

A summary of the antibacterial activity is illustrated in Tables 2-4, which show MIC_{90} values against a selection of clinically important bacteria. As an important indication for faropenem is likely to be respiratory tract infections, the activity against these organisms is discussed first.

Respiratory Tract Pathogens. Faropenem is active against the major bacterial causes of community-acquired respiratory tract infections. In a recent study, 4725 *S. pneumoniae*, 2614 *H. influenzae*, and 1193 *Moraxella catarrhalis* nonrepeat isolates were collected from patients across 273 hospitals in the United States.[43] Faropenem had similar MICs to those of imipenem against these isolates, some of which were β-lactamase producers, and had lower MICs than those of penicillin (*S. pneumoniae* isolates tested only), ampicillin, amoxicillin plus clavulanate, cefuroxime-axetil, ceftriaxone, trimethoprim-sulfamethoxazole, and levofloxacin. This indicates that faropenem may have utility in the outpatient treatment of respiratory infections, including those that are resistant to other therapies. The potent activity of faropenem may be due to its stability in the presence of β-lactamases produced by *H. influenzae* and *M. catarrhalis* strains.[44] Like other β-lactams, faropenem was not found to be active against atypical respiratory tract pathogens.[19]

Activity against drug-resistant strains also was investigated in a number of studies. In vitro activity was compared with that of 21 other antimicrobials against 385 genetically characterized isolates of *S. pneumoniae* resistant to tetracycline, trimethoprim-sulfamethoxazole, levofloxacin, erythromycin and clindamycin, or erythromycin but not clindamycin.[45] Faropenem was the most potent of all the agents tested, with an MIC_{90} of 0.25 mg/L or less. Significantly, faropenem expressed activity against isolates that were not susceptible to antimicrobials commonly used to treat pneumococcal infections. In another study, faropenem exhibited excellent activity against penicillin-susceptible, -intermediate, and -resistant *S. pneumoniae* (MIC_{50},

$_{90}$ = </= 0.015, 0.03; 0.12, 0.5; 1, and 1 mg/L, respectively), *H. influenzae* ($MIC_{50, 90}$ = 0.5, 1 mg/L), and *M. catarrhalis* ($MIC_{50, 90}$ = 0.12, 0.5 mg/L).[18]

In an in vitro study, faropenem was found to be highly stable to the group 2b β-lactamases TEM-1 and SHV-1, group 2be β-lactamases TEM-3 and TEM-9, and a penicillinase from *S. aureus* NCTC 11561.[46, 47]

Other Pathogens. Faropenem had lower MICs than those of amoxicillin plus clavulanate and second- and third-generation cephalosporins against most members of the Enterobacteriaceae (MICs </= 4 mg/L), as well as *Neisseria* sp, *E. faecalis*, streptococci, and β-lactamase-producing and non-β-lactamase-producing isolates of *H. influenzae* and *M. catarrhalis*.[48] Of the anaerobic bacteria studied, faropenem had the lowest MICs against *Clostridium perfringens* and peptostreptococci (MIC_{90} </= 1 mg/L), and *B. fragilis* (MIC_{90} = 4 mg/L). Faropenem exhibited reduced activity against *Serratia* sp, and activity was weak against *P. aeruginosa* and *S. maltophilia*. Faropenem was also found to be 4-8-fold more active against methicillin-susceptible *S. aureus* compared with amoxicillin, cefuroxime, and vancomycin, showing similar MICs as those of clindamycin (MIC_{90} = 0.25 mg/L).[49] In the same study, faropenem was found to be active in a subset of methicillin-resistant *S. aureus* strains (MIC_{90} = 2 mg/L, 18 isolates), although when all data were analyzed, the MIC_{90} was greater than 128 mg/L (31 isolates). For coagulase-negative staphylococci, faropenem was found to have an MIC_{90} of 1 mg/L.

Another group of authors showed that faropenem is active against unusual aerobic and anaerobic organisms isolated from bite wounds.[50] These included *Eikenella corrodens* (MIC_{90} = 0.25 mg/L) and *Pasteurella* sp (MIC_{90} = 0.25 mg/L).

Pharmacokinetics

In clinical trials, faropenem daloxate was administered at oral dosages of 300, 600, and 1200 mg twice/day. In these studies, the maximum concentration (C_{max}) was found to be approximately 13 mg/L (300-mg dose), half-life was 0.9-1.3 hours, urinary elimination accounted for 14-20% of the dose, and renal clearance was 1.6-2.9 L/hour (depending on patient's age and sex). Protein binding was approximately 95%, and metabolism involved the opening of the β-lactam ring to yield two diastereoisomers.[19] Coadministration with furosemide, probenecid (an inhibitor of tubular excretion), or antacids (which theoretically might inhibit the conversion of the daloxate to the free acid) did not produce any pharmacokinetic changes that warranted dosage adjustment.[51, 52]

Adverse events were similar to those seen with other β-lactams, but gastrointesinal effects were less common,[19] and headache was occasionally seen.[51, 52] In healthy volunteers, administration of faropenem did not result in the overgrowth of resistant microbial strains in the oropharynx, or select for *Clostridium difficile* or overgrowth of *Candida* or *P. aeruginosa*, or multiresistant Enterobacteriaceae in the feces.[51, 52]

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Cormican MG, Jones RN.

Department of Pathology, University of Iowa College of Medicine, Iowa City 52242, USA.

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[Abstract] [Full Text]

Chemical and Microbiologic Aspects of Penems, a D Class of β-Lactams: Focus on Faropenem

Author(s): Jeremy M. T. Hamilton-Miller, D.Sc., FRCPath[1]

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penems, ritipenem, sulopenem, MEN 10700, CGP 31608, faropenem

Abstract text

Many β-lactam antimicrobials were developed between the 1960s and 1980s, with continuing development driven by the resistance. Penems form a discrete class of β-lactams that comprises structural hybrids of penicillins (penams) and ceph The chemistry and microbiology of the representative penems MEN 10700, ritipenem, CGP 31608, sulopenem, BRL 427 reviewed. Particular emphasis is placed on faropenem, which is in late clinical development.

Author(s) affiliations

1. Department of Medical Microbiology, Royal Free and University College London Medical School, London, England. Address reprint requests to Jeremy M. T. Hamilton-Miller, D.Sc., FRCPath, Royal Free and University College Londo Free Campus, Rowland Hill Street, London NW3 2PF, United Kingdom; e-mail: j.hamilton-miller@ rfc.ucl.ac.uk.

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Confocal laser scanning microscopic observation of glycocalyx production by *Staphylococcus aureus* in skin lesions of bullous impetigo, atopic dermatitis and pemphigus foliaceus

Authors: Akiyama H.[1]; Hamada T.[1]; Huh W-K.[1]; Yamasaki O.[1]; Oono T.[1]; Fujimoto W.[1]; Iwatsuki K.[1]

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Summary

Background Glycocalyx collapses during dehydration to produce electron-dense accretions. Confocal laser scanning microscopy (CLSM) may be used to visualize fully hydrated microbial biofilms.

Objectives Using CLSM, to analyse glycocalyx production by *Staphylococcus aureus* cells in skin lesions of bullous impetigo, atopic dermatitis and pemphigus foliaceus. A second objective was to compare numbers of *S. aureus* cells in tissue sections prepared by different methods for routine light microscopy.

Methods S. aureus cells in skin lesions of impetigo, atopic dermatitis and pemphigus were stained with safranin, and positive staining with fluorescein isothiocyanate-conjugated concanavalin A was considered to indicate the presence of glycocalyx.

Results All *S. aureus* cells tested in skin lesions of impetigo, atopic dermatitis and pemphigus were covered with glycocalyx and formed microcolonies. The numbers of *S. aureus* cells in a routine light microscopy section were significantly lower than those in a frozen section that had not been dehydrated with ethanol.

Conclusions S. aureus cells generally produce glycocalyx in skin lesions of bullous impetigo, atopic dermatitis and pemphigus foliaceus, which accounts for the difficulty of removing *S. aureus* cells from these skin lesions. The glycocalyx may collapse during dehydration and most of the *S. aureus* cells may be carried away during preparation of routine light microscope sections.

Keywords: atopic dermatitis; bullous impetigo; confocal laser scanning microscopy; frozen section; glycocalyx; pemphigus foliaceus; Staphylococcus aureus

Document Type: Research article

DOI: 10.1046/j.1365-2133.2003.05162.x

Affiliations: 1: Department of Dermatology, Okayama University Graduate School of Medicine and Dentistry, Shikata-cho 2-5-1, Okayama 700-8558, Japan

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PATENT NUMBER	This data is not available for free
PATENT GRANT DATE	April 2, 2002
PATENT TITLE	Antibacterial composition for topical administration containing antibiotic
PATENT ABSTRACT	The present invention provides a safe antibacterial composition for topical administration which stably contains a penem antibiotic having a broad-spectrum and potent antibacterial activity while otherwise being chemically susceptible to hydrolysis, oxidation, photoisomerization or the like. The compositions of the present invention comprise an antibacterial composition for topical administration comprising a penem antibiotic or a pharmaceutically acceptable salt thereof in a non-aqueous base.
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PATENT FILE DATE	September 2, 1999
PATENT CT FILE DATE	January 12, 1999
PATENT CT NUMBER	This data is not available for free
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PATENT FOREIGN APPLICATION PRIORITY DATA	This data is not available for free
PATENT REFERENCES CITED	Woodward, R.B.; The chemical Society; London, Spec. No. 28, 1997, p. 167-180, "Recent Advances in the Chemistry . . . ". Kagaku Ryoho no Ryoiki, vol. 13 No. 10, 1997, p. 74-80. Chemotherapy vol. 42, S-1, 1994, p. 38-50. Japanese Journal of Chemotherapy (Nihon Kagaku Rhyoho Gakkai Zasshi), vol. 45 No. 11, 1997, p. 965-971.
PATENT PARENT CASE TEXT	This data is not available for free
PATENT CLAIMS	What is claimed is: 1. An antibacterial composition for topical administration comprising from 0.1 to 10% by weight, expressed as free anhydride on the basis of the entire composition, of (+)-(5R, 6S)-6-[(R)-1-hydroxyethyl]-7-oxo-3-[(R)-2-tetrahydrofuryl]-4-thia-1-azabic yclo[3.2.0]hepto-2-ene-2-carboxylic acid or a

pharmaceutically acceptable salt thereof, the balance consisting essentially of a non-aqueous hydrophobic base selected from the group of compounds consisting of hydrocarbon gel, paraffin, liquid paraffin, white petrolatum, hydrophilic petrolatum, petrolatum, microcrystalline wax, plant oils, carnauba wax, beeswax, stearic acid, stearyl alcohol, cacao butter, cetanol, hard fat, white ointment, simple ointment, ceresin and the composition of aminoalkyl methacrylate copolymer E, aminoalkyl methacrylate copolymer RS, methacrylic acid copolymer L, methacrylic acid copolymer S, ethyl acrylate methyl methacrylate copolymer emulsion.

2. The composition of claim 1 wherein the hydrophobic compound is a hydrocarbon gel or white petrolatum.

3. The composition of claim 1 further comprising one or more additives selected from gelatinizers, thickening agents, viscosifiers, viscosity enhancers and elasticizers incorporated in the non-aqueous base.

4. The composition of claim 1 further comprising one or more of water-soluble or hydrophilic polymer compounds incorporated in the non-aqueous base.

5. The composition of claim 4 wherein the water-soluble or hydrophilic polymer compound is one or more members selected from the group consisting of carmellose, carmellose sodium, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylic acid, sodium polyacrylate, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, xanthan gum, tragacanth gum, guar gum, locust bean gum, arabic gum, chitosan, sodium alginate, starches, gelatins, hydrophobic hydroxypropylmethylcellulose, which is incorporated at 0.1 to 10% by weight on the basis of the composition.

6. The composition of claim 1 for dermatological external use.

7. The composition of claim 1 for dental external use.

PATENT DESCRIPTION

FIELD OF THE INVENTION

The present invention relates to pharmaceutical compositions for use in dermatological, ophthalmologic, otolaryngologic, dental/oral surgical and urogenital fields, and more

specifically to the use of penem antibiotics for topical administration.

PRIOR ART

Ointments are used for topical administration to treat various diseases due to their convenience of administration and portability.

Therapeutic agents comprising antibiotics in an ointment base are useful for treating local inflammatory or pyogenic diseases caused by bacterial infection. There is a demand for these ointments, with a number being available.

For example, ointments containing aminoglycoside, tetracycline and chloramphenicol antibiotics are commonly used for inflammatory or pyogenic diseases in dermatological, ophthalmologic, otolaryngologic, dental/oral surgical and urogenital fields. Specific examples include commercially available dermatological agents for pyogenic diseases, based on aminoglycoside antibiotics such as kanamycin monosulfate ointments, tetracycline antibiotics such as tetracycline hydrochloride ointments and chloramphenicol antibiotics such as chloramphenicol ointments, as well as commercially available ophthalmic ointments based on macrolide antibiotics such as pimaricin formulations. Ointments containing tetracycline hydrochloride as a tetracycline antibiotic and hydrocortisone acetate are commercially available for dental/oral surgical application.

The active component in antibiotic ointments should be incorporated in a stable form. Japanese Patent Publication (Kokoku) No. 12728/89 describes a composition for topical administration as an external dental agent. In this composition, a magnesium compound is employed to a hydrogel comprising minocycline or a pharmaceutically acceptable salt thereof as a tetracycline antibiotic in a water-soluble polymer compound and a polyhydric alcohol to stabilize the antibiotic.

On the other hand, penem compounds are non-natural .beta.-lactam compounds designed based on the concept of combining the structures of penicillin and cephalosporin (e.g. see Woodward, R. B., In Recent Advances in the Chemistry of .beta.-Lactam Antibiotics; Elks, J., Ed; The Chemical Society; London, 1977; Spec. No. 28, pp. 167-180, Japanese Patent Public Disclosure (Kokai) Nos. 207387/86, 162694/88, 222486/85 and 119486/79), with the aim of creating a new range of antibiotics which have the broad antibacterial spectrum and high safety of penicillin antibiotics and cephem antibiotics belonging to .beta.-lactam antibiotics combined

with the potent antibacterial activity and high stability to .beta.-lactamase of carbapenem antibiotics.

Currently, sodium (+)-(5R, 6S)-6-[(R)-1-hydroxyethyl]-7-oxo-3-[(R)-2-tetrahydrofuryl]-4-thia-1-azabic yclo[3.2.0] hepto-2-ene-2-carboxylate 2.5 hydrate (faropenem sodium, hereinafter referred to as Compound 1) is orally administated as a therapeutic agent for use in various infections. The penem compounds are reported to show potent antibacterial activity on not only methicillin-sensitive Staphylococcus aureus (MSSA), Streptococcus pyrogenes and Streptococcus pneumoniae but also gram-positive bacteria less susceptible to conventional .beta.-lactam agents such as penicillin-resistant Streptococcus pneumoniae (PRSP), stomatic Streptococcus spp. and Enterococcus sp. by virtue of the novel skeleton called penem ring. The broad-spectrum antibacterial activity covers gram-negative bacteria such as Haemophilus influenzae and anaerobics such as the genus Bacteroides (Antibiotics & Chemotherapy, Vol. 13, No. 10, pp. 74-80, 1997). They are also reported to exhibit potent antibacterial activity on not only pathogenic bacteria of periodontitis such as Porphyromonas gingivalis (Chemotherapy, Vol. 42, S-1, pp. 38-50, 1994) but also other strains which are becoming increasingly resistant, that cause dental infections (Chemotherapy, Vol. 45, No. 11, pp. 965-971, 1997).

However, penem compounds, like other .beta.-lactam compounds, are generally chemically labile to hydrolysis, oxidation, photoisomerization, etc., and no composition for topical administration has been known that exhibits their excellent efficacy against inflammatory or pyogenic diseases, or diseases caused by infection with resistant bacteria.

Furthermore, in formulating ointments, an active component has to be mixed homogeneously throughout a semisolid base. When an active component is in the form of crystals or a crystalline powder like penem antibiotics, it is difficult to achieve overall homogeneity simply by dispersing the component in a base. Therefore, the component must first be ground into fine particles or dissolved in solvent; before being kneaded with a base into an ointment. Pulverization of the component is necessary also in view of the resulting texture of the formulation.

However, no technique for use of a penem compound as a component of an ointment has hitherto been known.

SUMMARY OF THE INVENTION

Under the circumstances described above, the inventors conducted extensive studies to develop a method to topically

administer penem antibiotics and pharmaceutically acceptable salts thereof which have a broad-spectrum and a potent antibacterial activity as well as being highly safe. As a result, the inventors have developed a highly safe antibacterial composition for topical administration in which the active component is incorporated in a stable form. The present invention has been accomplished based on the finding.

Accordingly, the present invention relates to an antibacterial composition for topical administration comprising a penem antibiotic or a pharmaceutically acceptable salt thereof incorporated in a non-aqueous base.

According to the present invention, very unstable penem antibiotics can be stably incorporated in a non-aqueous base such as hydrophobic polymer compounds to provide an antibacterial composition which can be widely used in dermatological, ophthalmologic, otolaryngologic, dental/oral surgical and urogenital fields.

Antibacterial compositions of the present invention may further contain various additives such as water-soluble or hydrophilic polymer compounds conferring thickening effects to provide various compositions for intended uses without affecting the stability of active components.

DETAILED DESCRIPTION OF THE INVENTION

The composition of the present invention is basically a viscous liquid or paste-like composition comprising a penem antibiotic or a pharmaceutically acceptable salt thereof incorporated in a non-aqueous base, and it is typically formulated into an ointment. It is important that the base of a non-aqueous type is used to ensure the stability of the penem antibiotic.

Penem antibiotics used in the present invention are not specifically limited provided that they are antibacterially active, compatible to lesions and safe in view of irritability, sensitizing effect and oral toxicity, and that they are pharmaceutically acceptable. They may be either in the form of a free carboxylic acid or a pharmaceutically acceptable salt including salts with alkali or alkali earth metals such as sodium, potassium, calcium, magnesium or amino acids such as lysine or ammonium salts. Examples of such compounds other than the above Compound 1 include those in which the substituent at position 3 is 1,4-dioxane-2-yl, ethylsulphanyl, 3-tetrahydrofurylmethyl, methoxymethyl or ((aminocarbonyl) oxy)methyl or the like. The content of such a compound in the composition may be appropriately determined depending on the nature of the compound, the disease to be treated or

other factors. For example, Compound 1 is incorporated at 10% by weight or less, normally 0.1 to 5% by weight expressed as free anhydride on the basis of the whole composition.

In order to formulate a penem antibiotic into an ointment, the active component must be incorporated into the composition in such a manner as to ensure the stability of the active component while assuring applicability or usability. In the present invention, proper stability can be ensured for penem antibiotics by using a non-aqueous base.

As used herein, "non-aqueous" base is a base which is substantially free from water. Thus, typical examples of non-aqueous bases are hydrophobic polymer compounds generally classified as hydrophobic ointment bases, such as oleaginous ointment bases consisting of hydrophobic polymers commonly used for ointments. Oleaginous ointment bases include, for example, hydrocarbon gel, paraffin, liquid paraffin, white petrolatum, petrolatum, microcrystalline wax, plant oils (vegetable oils), carnauba wax, beewax, stearic acid, stearyl alcohol, cacao butter, cetanol, hard fat, white ointment, simple ointment and ceresin.

Included in the non-aqueous bases used in the present invention are some emulsion bases which are free from any aqueous phase or film coating- or matrix -bases which are free from any aqueous phase. Emulsion ointment bases free from aqueous phase include hydrophilic petrolatum and purified lanolin. Film coatings and matrix bases free from any aqueous phase include acrylic resins which are commercially available under the trade name Eudragit (aminoalkyl methacrylate copolymer E, aminoalkyl methacrylate copolymer RS, methacrylic acid copolymer L, methacrylic acid copolymer S, ethyl acrylate.methyl methacrylate copolymer emulsion, available from Rohm Pharma, Germany) optionally in combination with plasticizers.

One or more of these bases are preferably used. Especially preferred are hydrocarbon gel, white petrolatum and Eudragit.

Neither hydrophilic bases in general nor many of the emulsion ointment bases, i.e. those comprising an aqueous phase, such as hydrophilic ointment and absorptive ointment will provide ointments which are capable of maintaining the activity of incorporated active components.

When the composition of the present invention is embodied as a pharmaceutical composition directly administered to a local site in the mouth for treating periodontitis, a high degree of

viscosity will be required to provide a prolonged effect at the target site. In such a case, additives such as gelatinizers, thickening agents, viscosifiers, viscosity enhancers and elasticizers may be optionally added. Additives for this purpose include water-soluble or hydrophilic polymer compounds such as carmellose, carmellose sodium, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylic acid, sodium polyacrylate, hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, hydroxyethylmethylcellulose, xanthan gum, tragacanth gum, guar gum, locust bean gum, arabic gum, chitosan, sodium alginate, starches, gelatins, hydrophobically modified-hydroxypropylmethylcellulose (Sangelose, available from Sankyo Chemical). One or more of these compounds can be added at a proportion of 0.1 to 10% by weight, preferably 0.5 to 10% by weight on the basis of the whole composition to further enhance the thickening effect at the target site.

The water-soluble or hydrophilic polymer compounds may also be employed to facilitate the absorption of secreted fluids from body tissues and prevent any contamination at the location.

As long as the purposes and effects of the present invention are not compromised, other components such as conventional plasticizers, surfactants, perfumes, flavoring agents or other additives may be optionally employed in an amount which does not influence the stability of the active component.

Suitable plasticizers include triacetine, diacetyl ethylene glycol, diethyl sebacate, diethyl phthalate, dibutyl phthalate, diisopropyl adipate, dibutyl succinate. Suitable surfactants include polyoxyl stearate 40, polyoxyethylene hydrogenated castor oil, polyoxyethylene polyoxypropylene glycol, Polysorbate, sucrose esters of fatty acids. Suitable flavoring agents include sodium, saccharin or the like. Stabilizers such as calcium disodium edetate or the like may also be used as judged appropriate.

The composition of the present invention may further contain appropriate amounts of perfumes such as menthol, carboxylic acids, anethole, eugenol, methyl salicylate, limonene, ocimene, citronellol, methyl acetate, methyl eugenol, vanillin, thymol, spearmint oil, peppermint oil, lemon oil, orange oil, rosemary oil, cinnamon oil, eucalyptus oil and pimento oil alone or in combination.

If necessary, higher alcohols, higher fatty acids, shellac-ethylcellulose, ethylcellulose, carnauba wax, hydroxypropylmethylcellulose acetate succinate and

solubilizing agents therefor may be used alone or in combination to effect control of the release of the active component from the base or to mask the odor of the active component.

The composition of the present invention comprise a base selected from those which have been confirmed in terms of their stability, and hence, which may be applied by various application methods without being limited to any specific one. For example, the ointment is suitable for any one of topical external application on the skin for the treatment of acne, urogenital application, oral application for the treatment of infectious periodontitis or the like.

In accordance with the present invention, it is also provided processes for preparing the composition of the invention.

The process of the invention is characterized in that a non-aqueous base is provided without any use of water in its preparation which would otherwise affect the stability of the active component. The process for preparing the composition of the present invention is described in detail below.

Three basic alternatives can be mentioned as methods for preparing the composition of the present invention, i.e., dispersion method, fusion method and slolubilizing method.

In the dispersion method, a homogeneous dispersion of the active component in a non-aqueous base is prepared by thoroughly grinding, pulverizing and kneading the active component, to make suitable the crystalline active component for topical administration. A preferred particle diameter of the active component is preferably 500 .mu.m or less, normally 100 .mu.m or less. For small scale production, the active component is mixed and thoroughly triturated with a portion of the base using an ointment slab and an ointment spatula or a mortar and a pestle. Subsequently, the rest of the base and other additives are added and trituration is continued until overall homogeneity is achieved. For large scale production, machines such as three roller machines, roll mills, kneaders, grinders or mixers are used. These machines may be used optionally under a reduced pressure or under heating. In such a case, the optimal stirring speed will be between 25 and 100 rpm and a preferred vacuum level ranges from 60 to 80 cmHg. A suitable heating temperature is between 35 to 60.degree. C. depending on the stability of the active component. If necessary, the resulted particles may be screened.

In the fusion method, since the active component is readily soluble in water, and its activity is lowered by hydrolysis, the

active component is first wet-triturated in a non-aqueous base such as a small amount of liquid paraffin. Subsequently, the other components are successively admixed in an order that increases the ability of the component to solubilize the active component, to thereby finally accomplish overall homogeneity. Fusion may be carried out under heating and stirring, if necessary. A suitable heating temperature is between 35 to 60.degree. C. depending on the stability of the active component. An ointment jar and a water bath may be used for small scale production, while machines such as a three roller machine, grinders and mixers will be used in a water bath for large scale production. During the process, an optimal stirring speed is between 25 to 100 rpm and a preferred vacuum level is 60 to 80 cmHg. Particles may be filtered or screened, if necessary.

The solubilizing method comprises the use of a non-aqueous solvent compatible with the non-aqueous base since the active component is readily soluble in water and its activity is lowered by hydrolysis. For example, a solution of the active component in methanol or ethanol is kneaded with a non-aqueous base, optionally under heating or stirring. A suitable heating temperature is between 35 to 60.degree. C. depending on the stability of the active component. The solution in which the active component has been dissolved is mixed and thoroughly triturated with a portion of the base, then further triturated with the rest of the base and other additives to provide overall homogeneity. Mixing or trituration is performed with an ointment slab and an ointment spatula or a mortar and a pestle for small scale production. For large scale production, a three roller machine, roller mills, kneaders, grinders and mixers or the like are used. These machines may be used optionally under reduced pressure and an optimal agitation speed is between 25 to 100 rpm and the vacuum level is preferably 60 to 80 cmHg. Optionally, particles may be filtered or screened.

The methods described above are p refer ably carried out under conditions which are free from not only water but also any other external factors which may potentially affect the stability of the active component. Such external factors include, for example, high temperatures, light and oxygen, which would all cause a deterioration in the active component.

The step of filling the composition into a container should also be carried out under conditions which are free from any of the stated external factors. Namely, the shape of the container should be capable of preventing contact with such external factors and also be able to properly maintain the stability of the active component of t he composition. Specific

examples include bottles or jars made from glass, plastics and synthetic resins, or tubes made from metals, plastics and laminates. To seal the container, a screw cap is used to effect closure for bottles and jars, or folding a metal tube filled from its bottom end or contact-bonding a similarly filled plastic tube between hot plates, or contact-bonding a similarly filled laminate tube under heat such as high frequency or supersonic wave can also be employed.

The shape of the container may be selected depending on the intended use. Thus, in addition to the shapes mentioned above, the container may have a shape which enables, for example, direct application or injection of the composition at various body sites. One example is a container designed to discharge the composition by a piston-like rod from an injection cylinder or a syringe made from plastic or synthetic resin

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